PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/008763	22.03.2004	24.03.2003

International Patent Classification (IPC) or both national classification and IPC
C12N5/00, C12N5/06, A61K45/00

Applicant
CASE WESTERN RESERVE UNIVERSITY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Vogt, T

Telephone No. +49 89 2399-8477

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

   see separate sheet

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 43-89, 90-141, 142-189 (IA)

because:

☒ the said international application, or the said claims Nos. 43-89, 90-141, 142-189 (IA) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4-12, 16-34, 36-38, 41-89, 105-111, 116-139 and 142-189
	No:	Claims	1-3, 13, 35, 39, 40, 90-95, 96-104,112-115, 140 and 141
Inventive step (IS)	Yes:	Claims	4-12, 16-34, 36-38, 41-89, 105-111, 116-139 and 142-189
	No:	Claims	1-3, 13, 35, 39, 40, 90-95, 96-104,112-115, 140 and 141
Industrial applicability (IA)	Yes:	Claims	1-42 and 96-141
	No:	Claims	43-95 and 142-189

2. Citations and explanations

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

II Priority.

It is noted that the invention as exemplified in D1 is word for word identical to that of the example of the present application. This raises doubt on the validity of the priority claim of the present application from the filing date of US-application 60/457151. At the time of writing this communication the priority document was not available to the examiner. The validity of the priority claim could therefore not be assessed.

III No opinion.

Claims 43-95, 142-189 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).
It is further noted that the ISR was restricted to compositions, and medical use thereof, obtained by a method comprising contacting a progenitor or stem cell with a targeting moiety.

V Reasoned Statement.

Subject matter of the present application.
The provision of a cell delivery composition, comprising a progenitor cell characterised in that the cell surface of said progenitor cell is modified with a tissue specific targeting moiety.

Cited prior art documents (Rule 64(1) PCT).

D1: WO 03/106640 A.
D2: CAPLAN ET AL. (2001) TRENDS IN MOL. MED. 7, 259-264.
D3: WO 00/23570 A.
D4: KIM ET AL. (1993) J. IMMUNOL. METH. 158, 57-65.
D5: WO 03/072542 A.
D6: US 2003/149235 A1.
D7: WO 02/090985 A.
D8: WO 03/009881 A.
D9: WO 02/20722 A.
D10: WO 01/92549 A.
D11: WO 99/46284 A.
D12: WO 98/53804 A.

D13: TREPEL ET AL. (2001) HUMAN GENE THER. 11, 1971-1981.
D14: SAMOYLOV ET AL. (2002) BIOMOL. ENGIN. 18, 269-272.
D15: AKERMAN ET AL. (2002) PNAS, USA 99, 12617-12621.

D1, D6 and D7 are not considered to form part of the prior art under Rule 64(1) PCT. It is noted that the designation fees for entry of D1 into the European regional phase were not yet paid at the time of writing this communication. Should the applicant pay said fees, then D1 will: I) be prejudicial to the novelty of the subject matter of the present application as indicated in the ISR, ii) introduce a lack of unity of invention and iii) raise doubt on the validity of the priority claim (see point I above).

Novelty (Art. 33(2) PCT).
Present claims 1, 90 and 96 relate in their broadest sense to a progenitor cell comprising a targeting moiety and the medical use thereof. This targeting moiety can be anything, including an endogenous cell surface protein. Since progenitor cells inherently find their way to a specific target tissue and therefore inherently have a targeting moiety, the subject matter of claims 1-3, 11-15, 35, 39, 40 lacks novelty 'a priori'. The subject matter of the corresponding use claims 90-95 and composition claims 96-104, 112-115, 140 and 141 lacks novelty for the same reason. It is noted that the use of a biocompatible scaffold is standard practice in therapy comprising stem or progenitor cells. An objection for a lack of unity of invention was not raised by the examiner, because this objection can easily be overcome. Moreover, it appears to have been the intention of the applicant that the progenitor cells must contain a non-endogenous targeting moiety. It would for instance be possible to overcome the above novelty objections by formulating a main method claim comprising the step of contacting/coating/linking of a progenitor cell with a targeting moiety (cf. claims 43(a) and 142(a)) and referring in all further claims to the progenitor cells obtained by said method.

D2 is a review on the use of stem cells in therapy. The attention of the applicant is directed to the passage starting at l. 12 on p. 262 "*The hypothesis was that ... considerable clinical benefit*".
It is stated: "*Increasing the efficiency of MSC engraftment and targeting the infused cells to specific tissue locations could have a large impact on future therapeutic uses of MSCs for other diseases.*" (p. 262, l. 20-24).
It is then continued: "*Methods to stimulate expression of specific cell surface ligands, either natural or engineered, that can mediate selective attachment to known receptors*

in target tissues of interest will be of considerable clinical benefit." (p. 262, l. 31-35). Thus D2 anticipates the modification of the cell surface to achieve specific targeting of progenitor or stem cells to specific tissues. It is noted that the term "*stimulate expression*" appears to include both genetic and non-genetic methods. However, D2 does not actually disclose or refer to any possible solutions on how to stimulate the expression of specific cell surface ligands.

D3-D15 are cited as examples of documents disclosing methods of targeting therapeutic agents to a specific tissue. They evidence that the targeting strategies used by the applicants are well known to public. D3-D15 are not prejudicial to the novelty of the presently claimed subject matter. Examples of targeting moieties include the modification of targeting moieties with lipophilic moieties, the use of a palmitoylated protein A/G linker-antibody system, and homing peptides obtained via eg. phage display.

To summarize: the subject matter of claims 1-3, 13, 35, 39, 40, 90-95, 96-104,112-115, 140 and 141 lack novelty (Art. 33(2) PCT).

Claims 4-12, 16-34, 36-38, 41-89, 105-111, 116-139 and 142-189 contain features which alone or in combination with the claims to which they refer do not appear to have been disclosed in the cited prior art. The subject matter of said claims therefore appears to be novel (Art. 33(2) PCT).

Inventive step (Art. 33(3) PCT).

The subject matter of novel claims 4-12, 16-34, 36-38, 41-89, 105-111, 116-139 and 142-189 all contain the feature that a progenitor cell is coated/contacted/linked with a targeting moiety.

D2 is considered to be the closest prior art. As indicated above D2 identifies the importance of modifying progenitors cells with a targeting moiety to home said progenitor cells to a target tissue.

The problem to be solved with the present application can therefore be seen as the provision of a method to home progenitor cells to target tissues.

D3 and D4 disclose both disclose methods for the modification of cell surfaces of living cells to achieve the delivery thereof to a target tissue. It however does not appear to be

obvious from D3 or D4 that progenitor or stem cells can be modified using the same method and that these cells maintain their biological function after this modification.

The examiner is therefore of the opinion that the subject matter of claims 4-12, 16-34, 36-38, 41-89, 105-111, 116-139 and 142-189 meets the requirements of inventive step.

Industrial applicability (Art. 33(4) PCT).
The subject matter of claims 1-42 and 96-141 meets the requirement of industrial applicability.

For the assessment of the present claims 43-95 and 142-189 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.